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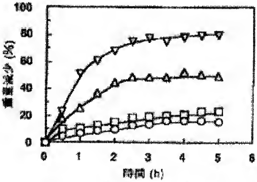
(54) TEMPERATURE RESPONSE-TYPE IN VIVO DEGRADABLE POLYMER

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a polymer which is degraded in vivo in response to plural pieces of vital information (an enzyme and a temperature).

SOLUTION: The objective polymer consists of a water soluble polymer having a three-dimensional network structure wherein a temperature-responsible polymer is introduced, as a graft chain, into an in vivo degradable polymer or a polymer having an in vivo degradable site in the molecule. As this polymer, of poly(N-isopropylacrylamide), polyacrylamide, polydimethylacrylamide, copolymers thereof, or a block copolymer of polyethylene glycol and polypropylene glycol are cited.



デキストラナーゼによるPBS中での3cの酵素分解：(○)：約30℃；(□)：約35℃；(△)：約37℃；(▽)：約40℃.

* NOTICES *

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CLAIMS

[Claim(s)]
[Claim 1]Temperature response type biodegradation nature Polymer Division, wherein temperature response Polymer Division is introduced into Polymer Division which is a water soluble polymer, has the three-dimensional network structure, and has a biodegradation nature part in biodegradation nature Polymer Division or a molecule as a graft chain.
[Claim 2]Temperature response type biodegradation nature Polymer Division of Claim 1 in which decomposition of a biodegradation nature Polymer Division chain or a biodegradation nature part occurs, and decomposition of the whole gel advances within a cell, tissue, an organ, or an organ in a time range which two sorts of different stimuli with enzyme discharge and a rise in heat generate simultaneously substantially on a disease unique target.
[Claim 3]Temperature response type biodegradation nature Polymer Division of Claim 1 in which decomposition of a biodegradation nature Polymer Division chain or a biodegradation nature part occurs, and decomposition of the whole gel advances within a site-specific cell which two sorts of different stimuli, enzyme discharge and a rise in heat, generate simultaneously substantially, an organization and an organ, and an organ.
[Claim 4]whole Polymer Division which has biodegradation nature Polymer Division or a biodegradation nature part, or its part is an oligopeptide chain or an oligosaccharide chain of biodegradation nature -- a disease -- one temperature response type biodegradation nature Polymer Division of the Claims 1-3 decomposed with a specific enzyme.
[Claim 5]Temperature response Polymer Division Poly (N-isopropylacrylamide), polyacrylamide, One temperature response type biodegradation nature Polymer Division of the Claims 1-4 which are polydimethyl acrylamide, these copolymers, or a block copolymer of a polyethylene glycol and a polypropylene glycol.
[Claim 6]A graft chain and a biodegradation nature polymer network of temperature response Polymer Division are dissolving below by body temperature, One temperature response type biodegradation nature Polymer Division of the Claims 1-5 in which both do phase separation and

zymolysis from a gel surface advances by a rise in heat by a disease although gel decomposition does not advance in this state with an enzyme which can disassemble biodegradation nature Polymer Division.

[Claim 7]As biodegradation nature Polymer Division which constitutes three-dimensional meshes of a net, Constituent amino acid An alanine, valine, leucine, isoleucine, methionine, Proline, phenylalanine, tryptophan, aspartic acid, glutamic acid, A glycine, serine, threonine, tyrosine, cystein, ricin, arginine, Histidine either An oligopeptide chain which is independent or consists of plurality, As a composition polysaccharide, or dextran, hyaluronic acid, a kitchen, chitosan, One temperature response type biodegradation nature Polymer Division of the Claims 1-6 in which it is an oligosaccharide chain which consists of alginic acid, chondroitin sulfate, starch, and pullulan, and each molecular weight before formation of the three-dimensional network structure is 500-1 million.

[Claim 8]One temperature response type biodegradation nature Polymer Division of the Claims 1-7 which make a water soluble polymer nondegradable [in the living body] a part of the composition.

[Claim 9]Temperature response type biodegradation nature Polymer Division of Claim 8 whose water soluble polymer nondegradable [in the living body] is polyether or polyether ester.

[Claim 10]As a biodegradation nature part which the molecular weight is 500-10000, and is included in the chain, a nondegradable water soluble polymer, A repeating unit is 1-5 and as constituent amino acid An alanine, valine, Leucine, isoleucine, methionine, proline, phenylalanine, Tryptophan, aspartic acid, glutamic acid, a glycine, serine, Threonine, tyrosine, cystein, ricin, arginine, and histidine either An oligopeptide chain which is independent or consists of plurality, Or Claim 8 which a repeating unit is 1-5 and has an oligosaccharide chain which consists of dextran, hyaluronic acid, a kitchen, chitosan, alginic acid, chondroitin sulfate, starch, and pullulan as a composition polysaccharide or 9 temperature response type biodegradation nature Polymer Division.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]The invention of this application relates to temperature response type biodegradation nature Polymer Division. It is related with still more detailed temperature response type biodegradation nature Polymer Division to which the invention of this application enables new drugs composition for a drug delivery system (DDS).
[0002]
[Description of the Prior Art]Many of biodegradation nature polymer materials aiming at an old drug delivery system were limited to the hydrophobic polymer material which releases gradually the drug dissolved or distributed in material by the biodegradation of material. In order for calling it it to also have realized drug release rate-limiting to disassembly of material, while controlling the drug diffusion in material and avoiding the drug break through at the time of un-decomposing, it was indispensable to have raised the instability (biodegradation nature) of material and to have limited hydrolysis of material near the surface, but. Usually, since it is based on hydrolysis enzymatic [the biodegradation of material], or nonenzymatic, in the former. While making the material itself into hydrophobicity as a result and restricting water-entry speed from the position which controls the infiltrating speed and hydrolysis rate to the inside of material, it is because the instability of the Polymer Division chain was increased and catabolic rate had to be gathered. However, this brought about the fall of the preservation stability as pharmaceutical preparation, and the fall of the biocompatibility at the time of the enthesis of material, and was to produce restriction in commercial production or an application site.
[0003]In recent years, only when living bodies, such as the time of a disease, need in consideration of a living body's homeostasis, the design of the intelligent pharmaceutical preparation which emits a drug is being attained using stimulus response nature Polymer Division. Controlling diffusion of a drug by the swelling-contraction action of the polymer material to a stimulus is mainly examined. But it was difficult to control drug release by the biodegradation

action of material with ON-OFF in this case. Then, the system which the stimulus response type resolvability of material is examined, recently answers a disease using active oxygen or some enzyme reactions, and sends a drug is becoming possible.

[0004]However, since various living body change has occurred in relation to mutual in the actual disease, it is high-risk to judge specification of a disease and its extent and to specify the amount of drug release by single living body change. Also in actual Medical Science Division, in order to specify a disease, the synthetic diagnostic function based on such a compound stimulus is needed also for the biodegradation mechanism of the polymer material which controls drug release as synthetic diagnosis is performed by two or more inspection items.

[0005]That is, in order to realize more advanced pharmacotherapy, realization of the drug carrier which has a complex diagnostic function and in which the enthesis is possible is indispensable, and the polymer material which answers two or more stimuli as leading methodology for it, and is disassembled in the living body is called for.

[0006]

[Means for Solving the Problem]An invention of this application takes an example by a problem of a biodegradation nature polymer material as a drug carrier from the former as above, A hydrophilic polymeric material (polymer hydrogel) which answers two or more living body change (temperature and enzyme), and is disassembled in the living body from a viewpoint that a stimulus response type polymer material which has a complex diagnostic function is called for is provided.

[0007]Namely, an invention of this application is a water soluble polymer, and has the three-dimensional network structure in the 1st, Temperature response type biodegradation nature Polymer Division, wherein temperature response Polymer Division is introduced into Polymer Division which has a biodegradation nature part in biodegradation nature Polymer Division or a molecule as a graft chain is provided. And an invention of this application about said Polymer Division to the 2nd within a cell, tissue, an organ, or an organ, In a time range generated simultaneously substantially, two sorts of different stimuli with enzyme discharge and a rise in heat on a disease unique target, Decomposition of a biodegradation nature Polymer Division chain or a biodegradation nature part occurs, and decomposition of the whole gel running temperature response type biodegradation nature Polymer Division to the 3rd. Two sorts of different stimuli, enzyme discharge and a rise in heat, within a site-specific cell generated simultaneously substantially, an organization and an organ, and an organ, Decomposition of a biodegradation nature Polymer Division chain or a biodegradation nature part occurs, and decomposition of the whole gel running temperature response type biodegradation nature Polymer Division to the 4th. The whole of Polymer Division which has biodegradation nature Polymer Division or a biodegradation nature part, or -- the part is an oligopeptide chain or an oligosaccharide chain of biodegradation nature -- a disease -- temperature response type biodegradation nature Polymer Division disassembled with a specific enzyme to the 5th. Temperature response Polymer Division provides temperature response type biodegradation nature Polymer Division which is poly (N-

isopropylacrylamide), polyacrylamide, polydimethyl acrylamide, these copolymers, or a block copolymer of a polyethylene glycol and a polypropylene glycol.

[0008]A graft chain and a biodegradation nature polymer network of temperature response Polymer Division are dissolving an invention of this application in the 6th below by body temperature, Although gel decomposition does not advance in this state with an enzyme which can disassemble biodegradation nature Polymer Division, Temperature response type biodegradation nature Polymer Division in which both do phase separation and zymolysis from a gel surface advances by a rise in heat by a disease to the 7th. As biodegradation nature Polymer Division which constitutes three-dimensional meshes of a net, Constituent amino acid An alanine, valine, leucine, isoleucine, methionine, Proline, phenylalanine, tryptophan, aspartic acid, glutamic acid, A glycine, serine, threonine, tyrosine, cystein, ricin, arginine, Histidine either An oligopeptide chain which is independent or consists of plurality, As a composition polysaccharide, or dextran, hyaluronic acid, a kitchen, chitosan, It is an oligosaccharide chain which consists of alginic acid, chondroitin sulfate, starch, and pullulan, Temperature response type biodegradation nature Polymer Division which makes a water soluble polymer nondegradable [in the living body] a part of the composition for temperature response type biodegradation nature Polymer Division in which each molecular weight is 500-1 million the 8th to the 9th, a water soluble polymer nondegradable [in the living body], Temperature response type biodegradation nature Polymer Division which is polyether or polyether ester to the 10th. As a biodegradation nature part which the molecular weight is 500-10000, and is included in the chain, a nondegradable water soluble polymer, A repeating unit is 1-5 and as constituent amino acid An alanine, valine, Leucine, isoleucine, methionine, proline, phenylalanine, Tryptophan, aspartic acid, glutamic acid, a glycine, serine, Threonine, tyrosine, cystein, ricin, arginine, and histidine either An oligopeptide chain which is independent or consists of plurality, Or a repeating unit is 1-5 and temperature response type biodegradation nature Polymer Division which has an oligosaccharide chain which consists of dextran, hyaluronic acid, a kitchen, chitosan, alginic acid, chondroitin sulfate, starch, and pullulan as a composition polysaccharide is provided.

[0009]

[Embodiment of the Invention]It is the feature that temperature response type biodegradation nature Polymer Division of an invention of this application forms the three-dimensional network structure into which a bridge is not constructed over the single Polymer Division chain like conventional biodegradation nature polymer hydrogel, and temperature response Polymer Division was first introduced as a graft chain rather than anything. This only enables not control of biodegradation speed but qualitative control of biodegradation. That is, only by the enzyme of the disease origin which decomposes a polymer network existing, approach of an enzyme is barred by the solid injury based on a graft chain, and decomposition does not advance as a result according to it. On the other hand, if temperature rises according to a disease with existence of an enzyme, for example, a graft chain will contract, phase separation will be carried out to three-

dimensional meshes of a net, the approach to the meshes of a net of an enzyme will become easy, and hydrolysis will advance one by one from a gel surface. Thus, when the dialytic ferment and rise in heat as a stimulus exist independently, it does not decompose, but only when two exist simultaneously, it decomposes. Therefore, compared with the polymer gel decomposed by the conventional independent stimulus, temperature response type biodegradation nature Polymer Division of this invention can recognize a more synthetic living body change, and has an advantage which can control biodegradation nature qualitatively.

[0010]Thus, in this temperature response type biodegradation nature Polymer Division, qualitative alteration of zymolysis nature is made possible by the structure where temperature response Polymer Division was introduced as a graft chain. The intelligent pharmaceutical preparation which has a complex diagnostic function by this, and the application to a medical-application micromachine are expected. By this invention, the design of the pharmaceutical preparation which realizes drug delivery based on synthetic diagnoses, such as a kind, a grade, etc. of a disease, is especially attained in wide range routes of administration, such as intravenous injection, taking orally, and hypodermic enthesis.

[0011]If the composition of temperature response type biodegradation nature Polymer Division of this invention is explained in more detail, first -- the parts of the both ends of whole Polymer Division or Polymer Division etc. which constitute three-dimensional meshes of a net are biodegradation nature Polymer Division, such as oligopeptides or oligosaccharide, -- a disease -- being decomposed by the specific enzyme is appropriate. As biodegradation nature Polymer Division which constitutes such three-dimensional meshes of a net, Constituent amino acid as aforementioned An alanine, valine, leucine, isoleucine, Methionine, proline, phenylalanine, tryptophan, aspartic acid, Glutamic acid, a glycine, serine, threonine, tyrosine, cystein, Ricin, arginine, and histidine either The oligopeptide chain which is independent or consists of plurality, As a composition polysaccharide, or dextran, hyaluronic acid, a kitchen, chitosan, It is an oligosaccharide chain which consists of alginic acid, chondroitin sulfate, starch, and pullulan, and each molecular weight before formation of the three-dimensional network structure is illustrated as 500-1 million and what has that suitable it is 5000-100000 desirably.

[0012]In Polymer Division of this invention, nondegradable Polymer Division, for example, polyether, polyether ester, etc. may contain as that part. For example, when using nondegradable water soluble polymers, such as a polyethylene glycol, the molecular weight, As 500-10000 and a biodegradation nature part which is 1000-5000 desirably and is included in the chains, such as both ends, A repeating unit is 1-5 and as constituent amino acid An alanine, valine, Leucine, isoleucine, methionine, proline, phenylalanine, Tryptophan, aspartic acid, glutamic acid, a glycine, serine, Threonine, tyrosine, cystein, ricin, arginine, and histidine either The oligopeptide chain which is independent or consists of plurality, Or a repeating unit is 1-5 and it is preferred to have an oligosaccharide chain which consists of dextran, hyaluronic acid, a kitchen, chitosan, alginic acid, chondroitin sulfate, starch, and pullulan as a composition polysaccharide.

[0013]As temperature response Polymer Division, poly (N-isopropylacrylamide), polyacrylamide, polydimethyl acrylamide, these copolymers, or the block copolymer of a polyethylene glycol and a polypropylene glycol is mentioned as a suitable thing. Although these temperature response Polymer Division is introduced as a graft chain, about the graft chain length, 1000-100000 and the thing which serves as the range of 2000-10000 desirably are taken into consideration as a molecular weight.

[0014]The temperature response Polymer Division graft chain and the biodegradation nature polymer network are dissolving below by body temperature especially, Although gel decomposition does not advance in this state with the enzyme which can disassemble biodegradation nature Polymer Division, it is desirable to constitute this graft chain and degradable polymer so that both may do phase separation and the zymolysis from a gel surface may advance as a result by the rise in heat by a disease.

[0015]Above temperature response type biodegradation nature Polymer Division of this invention can take into consideration and manufacture various kinds of polymerization methods known conventionally and its condition. The same may be said of introduction of said graft chain. For example, to the crosslinking method which fabricates the three-dimensional network structure, all the crosslinking methods of polysaccharide generally known are applied. Below-mentioned working example also shows the one method, and the method of introducing a double bond like an methacrylic group and constructing a bridge by a radical reaction, the crosslinking method by an addition reaction with the diisocyanate compound reacted to the hydroxyl group which exists in polysaccharide, etc. are adopted suitably.

[0016]Then, working example is shown below and this invention is explained to it in more detail.

[0017]

[Example](Working example 1)

The aminoethane thiol which is a chain transfer agent of the synthetic specified quantity of the N-isopropylacrylamide (IPAAm)-N,N-dimethylacrylamide (DMAAm) copolymer (1) which has an amino group in <A> one end, Azobisiso BUCHIRO acrylonitrile (azobisuisobutironitoriru) which is a radical initiator and IPAAm (8.2 g, 72mmol), and DMAAm (1.8 g, 18mmol) were dissolved in DMF, and it was considered as the homogeneous solution. After carrying out the radical polymerization of this solution according to a nitrogen atmosphere at 75 ** for 15 hours, the solution was invested in diethylether and the copolymer was isolated. The number average molecular weight was computed by titration by a perchloric acid-acetic acid standard solution, using crystal violet as an indicator (Table 1). Minimum critical solution temperature (LCST) was performed by observing transmittance change of 500-nm visible light. Drawing 1 shows the result.

[0018]The molecular weights of 1 which the chain transfer agent and the monomer concentration ratio were changed, and was compounded were 2600, 4200, and 8800, respectively. From ^{1}H-NMR measurement, the IPAAm content of all the copolymers was 0.7. As transmittance change in the phosphoric acid buffer solution (PBS) at 500 nm by the temperature change of drawing 1 saw,

no LCST of IPAAm copolymers depended also on molecular weights differing, but was near 35 **.

[0019]

[Table 1]

片末端にアミノ基を有するIPAAm/DMAAm共重合体の合成[a)]

試料	[S]/[M][b)]	添加率 (%)	数平均分子量 ($\overline{Mn}$)[c)]
1a	0.050	63	2600
1b	0.010	71	4200
1c	0.0043	62	8800

a) AIBN濃度、0.1mol%モノマー

b) [S]：連鎖移動剤濃度、[M]：モノマー濃度

c) 末端アミノ基の滴定による数平均分子量

[0020]An excessive amount of triethylamines were dissolved in DMF as the copolymer (1), (5g), methacrylic acid chloride (2 ml), and acid acceptance agent of composition <A> of an IPAAm-DMAAm copolymer (2) which have an methacrylic group in <B> one end, and it stirred at 4 ** for 24 hours. The solution was invested in diethylether after ending reaction, and 2 was isolated. The copolymer (2) of composition <B> of the dextran hydrogel (3) which has <C>IPAAm-DMAAm copolymer as a graft chain, (0.3g), Methacrylic-ized dextran (Ma-Dex) (0.7g) and ammonium persulfate (APS) (50 mg) were dissolved in DMSO3ml, and the homogeneous solution was prepared. After both sides fed this solution into the spacer for gel production covered with glass, the optical exposure was carried out at the room temperature for 4 hours using the high-pressure mercury-vapor lamp. Hydrogel was invested in distilled water after ending reaction, and equilibrium swelling was carried out for ten days at the room temperature.

[0021]The molecular weight showed drawing 2 degree-of-swelling change of the hydrogel respectively accompanying [as 3a, 3b, and 3c] the temperature change in the inside of PBS for the dextran hydrogel which has an IPAAm copolymer of 2600, 4200, and 8800 as a graft chain. The degree of swelling of all the hydrogels was constant in the range of ten to 45 **. The degree of swelling of hydrogel was so large that the molecular weight of the graft chain in hydrogel was low. The temperature dependence of the transmittance of the hydrogel in a swollen state is shown in drawing 3. The transmittance of all the hydrogels increased by falling with a rise in heat and reducing temperature.

(Working example 2)

The hydrogel (20x20x2 mm) obtained by working example 1 which cut out the IPAAm-DMAAm copolymer to the analysis plate-like (20x20x2 mm) of the decomposition action of the dextran hydrogel which it has as a graft chain, It was immersed in the dextranase content phosphoric acid buffer solution (pH 7.4) of prescribed temperature, and the weight change was measured

temporally. The enzyme activity of the dextranase at a different temperature was searched for from the zymolysis speed of dextran at each temperature, and the decomposition experiment of hydrogel was prepared so that enzyme activity might become the same at each temperature.

[0022]Although said 3a was thoroughly decomposed also in which [of 30 to 40 **] temperature requirement, the temperature dependence of zymolysis nature was not accepted (drawing 4). Although 3b was thoroughly decomposed in not less than 35 **, in 30 **, decomposition stopped [4 hours and 30 minutes] afterward (drawing 5). Although decomposition of 3c did not advance thoroughly at which temperature, the temperature dependence of the zymolysis nature was accepted (drawing 6). The zymolysis nature of hydrogel was evaluated using the decomposition index of a following formula.

[0023]Decomposition index (%) =A/Aox100 (Ao: standard accumulation volume of decomposition, accumulation volume of the decomposition obtained from A:experiment)

Drawing 7 illustrates the feature of calculation of a decomposition index, and drawing 8 shows the relation of the decomposition index and temperature which were calculated. The decomposition index of 3a was constant also at which temperature. The decomposition index of 3b and 3c increased with the rise in heat.

[0024]

[Effect of the Invention]Since it decomposes in the living body according to two or more stimuli (an enzyme and temperature), only by the drug contained in gel answering a compound stimulus, in temperature response type biodegradation nature Polymer Division of an invention of this application, it is emitted, as explained in detail above. That is, after diagnosing the information of living bodies, such as a kind, a grade, etc. of a disease, synthetically, the medication what is called by compound diagnosis which specifies the amount of drug release needed becomes possible with the function of biodegradation nature hydrogel itself. It is expected that pharmacotherapy with high validity to various kinds of diseases, such as a therapy based on advanced diagnosis of the disease or a therapy of a complex disease which is accompanied by various complication, becomes possible by this. Since the site-specific biodegradation nature in which a complex stimulus exists is also realizable, the application as a medical-application micromachine which carries out medical practice by a specific part in the living body is also expected.

[Translation done.]

TECHNICAL FIELD

[Field of the Invention]The invention of this application relates to temperature response type biodegradation nature Polymer Division. It is related with still more detailed temperature response type biodegradation nature Polymer Division to which the invention of this application enables new drugs composition for a drug delivery system (DDS).

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EFFECT OF THE INVENTION

[Effect of the Invention]Since it decomposes in the living body according to two or more stimuli (an enzyme and temperature), only by the drug contained in gel answering a compound stimulus, in temperature response type biodegradation nature Polymer Division of an invention of this application, it is emitted, as explained in detail above. That is, after diagnosing the information of living bodies, such as a kind, a grade, etc. of a disease, synthetically, the medication what is called by compound diagnosis which specifies the amount of drug release needed becomes possible with the function of biodegradation nature hydrogel itself. It is expected that pharmacotherapy with high validity to various kinds of diseases, such as a therapy based on advanced diagnosis of the disease or a therapy of a complex disease which is accompanied by various complication, becomes possible by this. Since the site-specific biodegradation nature in which a complex stimulus exists is also realizable, the application as a medical-application micromachine which carries out medical practice by a specific part in the living body is also expected.

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TECHNICAL PROBLEM

[Description of the Prior Art]Many of biodegradation nature polymer materials aiming at an old drug delivery system were limited to the hydrophobic polymer material which releases gradually the drug dissolved or distributed in material by the biodegradation of material. In order for calling it it to also have realized drug release rate-limiting to disassembly of material, while controlling the drug diffusion in material and avoiding the drug break through at the time of un-decomposing, it was indispensable to have raised the instability (biodegradation nature) of material and to have limited hydrolysis of material near the surface, but. Usually, since it is based on hydrolysis enzymatic [the biodegradation of material], or nonenzymatic, in the former. While making the material itself into hydrophobicity as a result and restricting water-entry speed from the position which controls the infiltrating speed and hydrolysis rate to the inside of material, it is because the instability of the Polymer Division chain was increased and catabolic rate had to be gathered. However, this brought about the fall of the preservation stability as pharmaceutical preparation, and the fall of the biocompatibility at the time of the enthesis of material, and was to produce restriction in commercial production or an application site.
[0003]In recent years, only when living bodies, such as the time of a disease, need in consideration of a living body's homeostasis, the design of the intelligent pharmaceutical preparation which emits a drug is being attained using stimulus response nature Polymer Division. Controlling diffusion of a drug by the swelling-contraction action of the polymer material to a stimulus is mainly examined. But it was difficult to control drug release by the biodegradation action of material with ON-OFF in this case. Then, the system which the stimulus response type resolvability of material is examined, recently answers a disease using active oxygen or some enzyme reactions, and sends a drug is becoming possible.
[0004]However, since various living body change has occurred in relation to mutual in the actual disease, it is high-risk to judge specification of a disease and its extent and to specify the amount of drug release by single living body change. Also in actual Medical Science Division, in order to specify a disease, the synthetic diagnostic function based on such a compound stimulus is

needed also for the biodegradation mechanism of the polymer material which controls drug release as synthetic diagnosis is performed by two or more inspection items.

[0005]That is, in order to realize more advanced pharmacotherapy, realization of the drug carrier which has a complex diagnostic function and in which the enthesis is possible is indispensable, and the polymer material which answers two or more stimuli as leading methodology for it, and is disassembled in the living body is called for.

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MEANS

[Means for Solving the Problem]An invention of this application takes an example by a problem of a biodegradation nature polymer material as a drug carrier from the former as above, A hydrophilic polymeric material (polymer hydrogel) which answers two or more living body change (temperature and enzyme), and is disassembled in the living body from a viewpoint that a stimulus response type polymer material which has a complex diagnostic function is called for is provided. [0007]Namely, an invention of this application is a water soluble polymer, and has the three-dimensional network structure in the 1st, Temperature response type biodegradation nature Polymer Division, wherein temperature response Polymer Division is introduced into Polymer Division which has a biodegradation nature part in biodegradation nature Polymer Division or a molecule as a graft chain is provided. And an invention of this application about said Polymer Division to the 2nd within a cell, tissue, an organ, or an organ, In a time range generated simultaneously substantially, two sorts of different stimuli with enzyme discharge and a rise in heat on a disease unique target, Decomposition of a biodegradation nature Polymer Division chain or a biodegradation nature part occurs, and decomposition of the whole gel running temperature response type biodegradation nature Polymer Division to the 3rd. Two sorts of different stimuli, enzyme discharge and a rise in heat, within a site-specific cell generated simultaneously substantially, an organization and an organ, and an organ, Decomposition of a biodegradation nature Polymer Division chain or a biodegradation nature part occurs, and decomposition of the whole gel running temperature response type biodegradation nature Polymer Division to the 4th. The whole of Polymer Division which has biodegradation nature Polymer Division or a biodegradation nature part, or -- the part is an oligopeptide chain or an oligosaccharide chain of biodegradation nature -- a disease -- temperature response type biodegradation nature Polymer Division disassembled with a specific enzyme to the 5th. Temperature response Polymer Division provides temperature response type biodegradation nature Polymer Division which is poly (N-isopropylacrylamide), polyacrylamide, polydimethyl acrylamide, these copolymers, or a block copolymer of a polyethylene glycol and a polypropylene glycol.

[0008]A graft chain and a biodegradation nature polymer network of temperature response Polymer Division are dissolving an invention of this application in the 6th below by body temperature, Although gel decomposition does not advance in this state with an enzyme which can disassemble biodegradation nature Polymer Division, Temperature response type biodegradation nature Polymer Division in which both do phase separation and zymolysis from a gel surface advances by a rise in heat by a disease to the 7th. As biodegradation nature Polymer Division which constitutes three-dimensional meshes of a net, Constituent amino acid An alanine, valine, leucine, isoleucine, methionine, Proline, phenylalanine, tryptophan, aspartic acid, glutamic acid, A glycine, serine, threonine, tyrosine, cystein, ricin, arginine, Histidine either An oligopeptide chain which is independent or consists of plurality, As a composition polysaccharide, or dextran, hyaluronic acid, a kitchen, chitosan, It is an oligosaccharide chain which consists of alginic acid, chondroitin sulfate, starch, and pullulan, Temperature response type biodegradation nature Polymer Division which makes a water soluble polymer nondegradable [in the living body] a part of the composition for temperature response type biodegradation nature Polymer Division in which each molecular weight is 500-1 million the 8th to the 9th, a water soluble polymer nondegradable [in the living body], Temperature response type biodegradation nature Polymer Division which is polyether or polyether ester to the 10th. As a biodegradation nature part which the molecular weight is 500-10000, and is included in the chain, a nondegradable water soluble polymer, A repeating unit is 1-5 and as constituent amino acid An alanine, valine, Leucine, isoleucine, methionine, proline, phenylalanine, Tryptophan, aspartic acid, glutamic acid, a glycine, serine, Threonine, tyrosine, cystein, ricin, arginine, and histidine either An oligopeptide chain which is independent or consists of plurality, Or a repeating unit is 1-5 and temperature response type biodegradation nature Polymer Division which has an oligosaccharide chain which consists of dextran, hyaluronic acid, a kitchen, chitosan, alginic acid, chondroitin sulfate, starch, and pullulan as a composition polysaccharide is provided.

[0009]

[Embodiment of the Invention]It is the feature that temperature response type biodegradation nature Polymer Division of an invention of this application forms the three-dimensional network structure into which a bridge is not constructed over the single Polymer Division chain like conventional biodegradation nature polymer hydrogel, and temperature response Polymer Division was first introduced as a graft chain rather than anything. This only enables not control of biodegradation speed but qualitative control of biodegradation. That is, only by the enzyme of the disease origin which decomposes a polymer network existing, approach of an enzyme is barred by the solid injury based on a graft chain, and decomposition does not advance as a result according to it. On the other hand, if temperature rises according to a disease with existence of an enzyme, for example, a graft chain will contract, phase separation will be carried out to three-dimensional meshes of a net, the approach to the meshes of a net of an enzyme will become easy, and hydrolysis will advance one by one from a gel surface. Thus, when the dialytic ferment

and rise in heat as a stimulus exist independently, it does not decompose, but only when two exist simultaneously, it decomposes. Therefore, compared with the polymer gel decomposed by the conventional independent stimulus, temperature response type biodegradation nature Polymer Division of this invention can recognize a more synthetic living body change, and has an advantage which can control biodegradation nature qualitatively.

[0010]Thus, in this temperature response type biodegradation nature Polymer Division, qualitative alteration of zymolysis nature is made possible by the structure where temperature response Polymer Division was introduced as a graft chain. The intelligent pharmaceutical preparation which has a complex diagnostic function by this, and the application to a medical-application micromachine are expected. By this invention, the design of the pharmaceutical preparation which realizes drug delivery based on synthetic diagnoses, such as a kind, a grade, etc. of a disease, is especially attained in wide range routes of administration, such as intravenous injection, taking orally, and hypodermic enthesis.

[0011]If the composition of temperature response type biodegradation nature Polymer Division of this invention is explained in more detail, first -- the parts of the both ends of whole Polymer Division or Polymer Division etc. which constitute three-dimensional meshes of a net are biodegradation nature Polymer Division, such as oligopeptides or oligosaccharide, -- a disease -- being decomposed by the specific enzyme is appropriate. As biodegradation nature Polymer Division which constitutes such three-dimensional meshes of a net, Constituent amino acid as aforementioned An alanine, valine, leucine, isoleucine, Methionine, proline, phenylalanine, tryptophan, aspartic acid, Glutamic acid, a glycine, serine, threonine, tyrosine, cystein, Ricin, arginine, and histidine either The oligopeptide chain which is independent or consists of plurality, As a composition polysaccharide, or dextran, hyaluronic acid, a kitchen, chitosan, It is an oligosaccharide chain which consists of alginic acid, chondroitin sulfate, starch, and pullulan, and each molecular weight before formation of the three-dimensional network structure is illustrated as 500-1 million and what has that suitable it is 5000-100000 desirably.

[0012]In Polymer Division of this invention, nondegradable Polymer Division, for example, polyether, polyether ester, etc. may contain as that part. For example, when using nondegradable water soluble polymers, such as a polyethylene glycol, the molecular weight, As 500-10000 and a biodegradation nature part which is 1000-5000 desirably and is included in the chains, such as both ends, A repeating unit is 1-5 and as constituent amino acid An alanine, valine, Leucine, isoleucine, methionine, proline, phenylalanine, Tryptophan, aspartic acid, glutamic acid, a glycine, serine, Threonine, tyrosine, cystein, ricin, arginine, and histidine either The oligopeptide chain which is independent or consists of plurality, Or a repeating unit is 1-5 and it is preferred to have an oligosaccharide chain which consists of dextran, hyaluronic acid, a kitchen, chitosan, alginic acid, chondroitin sulfate, starch, and pullulan as a composition polysaccharide.

[0013]As temperature response Polymer Division, poly (N-isopropylacrylamide), polyacrylamide, polydimethyl acrylamide, these copolymers, or the block copolymer of a polyethylene glycol and a

polypropylene glycol is mentioned as a suitable thing. Although these temperature response Polymer Division is introduced as a graft chain, about the graft chain length, 1000-100000 and the thing which serves as the range of 2000-10000 desirably are taken into consideration as a molecular weight.

[0014]The temperature response Polymer Division graft chain and the biodegradation nature polymer network are dissolving below by body temperature especially, Although gel decomposition does not advance in this state with the enzyme which can disassemble biodegradation nature Polymer Division, it is desirable to constitute this graft chain and degradable polymer so that both may do phase separation and the zymolysis from a gel surface may advance as a result by the rise in heat by a disease.

[0015]Above temperature response type biodegradation nature Polymer Division of this invention can take into consideration and manufacture various kinds of polymerization methods known conventionally and its condition. The same may be said of introduction of said graft chain. For example, to the crosslinking method which fabricates the three-dimensional network structure, all the crosslinking methods of polysaccharide generally known are applied. Below-mentioned working example also shows the one method, and the method of introducing a double bond like an methacrylic group and constructing a bridge by a radical reaction, the crosslinking method by an addition reaction with the diisocyanate compound reacted to the hydroxyl group which exists in polysaccharide, etc. are adopted suitably.

[0016]Then, working example is shown below and this invention is explained to it in more detail.

[Translation done.]

* NOTICES *

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EXAMPLE

[Example](Working example 1)
The aminoethane thiol which is a chain transfer agent of the synthetic specified quantity of the N-isopropylacrylamide (IPAAm)-N,N-dimethylacrylamide (DMAAm) copolymer (1) which has an amino group in <A> one end, Azobisiso BUCHIRO acrylonitrile (azobisuisobutironitoriru) which is a radical initiator and IPAAm (8.2 g, 72mmol), and DMAAm (1.8 g, 18mmol) were dissolved in DMF, and it was considered as the homogeneous solution. After carrying out the radical polymerization of this solution according to a nitrogen atmosphere at 75 ** for 15 hours, the solution was invested in diethylether and the copolymer was isolated. The number average molecular weight was computed by titration by a perchloric acid-acetic acid standard solution, using crystal violet as an indicator (Table 1). Minimum critical solution temperature (LCST) was performed by observing transmittance change of 500-nm visible light. Drawing 1 shows the result.
[0018]The molecular weights of 1 which the chain transfer agent and the monomer concentration ratio were changed, and was compounded were 2600, 4200, and 8800, respectively. From ^{1}H-NMR measurement, the IPAAm content of all the copolymers was 0.7. As transmittance change in the phosphoric acid buffer solution (PBS) at 500 nm by the temperature change of drawing 1 saw, no LCST of IPAAm copolymers depended also on molecular weights differing, but was near 35 **.
[0019]
[Table 1]

片末端にアミノ基を有するIPAAm/DMAAm共重合体の合成[a)]

試料	[S]/[M][b)]	添加率 (%)	数平均分子量 ($\overline{Mn}$)[c)]
1a	0.050	63	2600
1b	0.010	71	4200
1c	0.0043	62	8800

a) AIBN濃度、0.1mol%モノマー

b) [S]：連鎖移動剤濃度、[M]：モノマー濃度

c) 末端アミノ基の滴定による数平均分子量

[0020]An excessive amount of triethylamines were dissolved in DMF as the copolymer (1), (5g), methacrylic acid chloride (2 ml), and acid acceptance agent of composition <A> of an IPAAm-DMAAm copolymer (2) which have an methacrylic group in <B> one end, and it stirred at 4 ** for 24 hours. The solution was invested in diethylether after ending reaction, and 2 was isolated. The copolymer (2) of composition <B> of the dextran hydrogel (3) which has <C>IPAAm-DMAAm copolymer as a graft chain, (0.3g), Methacrylic-ized dextran (Ma-Dex) (0.7g) and ammonium persulfate (APS) (50 mg) were dissolved in DMSO3ml, and the homogeneous solution was prepared. After both sides fed this solution into the spacer for gel production covered with glass, the optical exposure was carried out at the room temperature for 4 hours using the high-pressure mercury-vapor lamp. Hydrogel was invested in distilled water after ending reaction, and equilibrium swelling was carried out for ten days at the room temperature.

[0021]The molecular weight showed drawing 2 degree-of-swelling change of the hydrogel respectively accompanying [as 3a, 3b, and 3c] the temperature change in the inside of PBS for the dextran hydrogel which has an IPAAm copolymer of 2600, 4200, and 8800 as a graft chain. The degree of swelling of all the hydrogels was constant in the range of ten to 45 **. The degree of swelling of hydrogel was so large that the molecular weight of the graft chain in hydrogel was low. The temperature dependence of the transmittance of the hydrogel in a swollen state is shown in drawing 3. The transmittance of all the hydrogels increased by falling with a rise in heat and reducing temperature.

(Working example 2)

The hydrogel (20x20x2 mm) obtained by working example 1 which cut out the IPAAm-DMAAm copolymer to the analysis plate-like (20x20x2 mm) of the decomposition action of the dextran hydrogel which it has as a graft chain, It was immersed in the dextranase content phosphoric acid buffer solution (pH 7.4) of prescribed temperature, and the weight change was measured temporally. The enzyme activity of the dextranase at a different temperature was searched for from the zymolysis speed of dextran at each temperature, and the decomposition experiment of hydrogel was prepared so that enzyme activity might become the same at each temperature.

[0022]Although said 3a was thoroughly decomposed also in which [of 30 to 40 **] temperature requirement, the temperature dependence of zymolysis nature was not accepted (drawing 4). Although 3b was thoroughly decomposed in not less than 35 **, in 30 **, decomposition stopped [4 hours and 30 minutes] afterward (drawing 5). Although decomposition of 3c did not advance thoroughly at which temperature, the temperature dependence of the zymolysis nature was accepted (drawing 6). The zymolysis nature of hydrogel was evaluated using the decomposition index of a following formula.

[0023]Decomposition index (%) =A/Aox100 (Ao: standard accumulation volume of decomposition, accumulation volume of the decomposition obtained from A:experiment)

Drawing 7 illustrates the feature of calculation of a decomposition index, and drawing 8 shows the relation of the decomposition index and temperature which were calculated. The decomposition index of 3a was constant also at which temperature. The decomposition index of 3b and 3c increased with the rise in heat.

[Translation done.]

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1]It is a figure showing the temperature dependence of the transmittance of an IPAAm-DMAAm copolymer which has an one end amino group as working example.
[Drawing 2]It is a figure showing the temperature dependence of the degree of swelling of the Dex hydrogel which uses an IPAAm-DMAAm copolymer as a graft chain.
[Drawing 3]It is a figure showing the temperature dependence of the transmittance of Dex hydrogel in relation to drawing 2.
[Drawing 4]It is a figure showing the zymolysis action of the Dex hydrogel (3a) as working example.
[Drawing 5]It is a figure showing the zymolysis action of Dex hydrogel (3b).
[Drawing 6]It is a figure showing the zymolysis action of Dex hydrogel (3c).
[Drawing 7]It is a figure showing calculation of a decomposition index.
[Drawing 8]It is a figure showing the relation between the decomposition index of Dex hydrogel (3a, 3b, 3c), and temperature.

[Translation done.]

* NOTICES *

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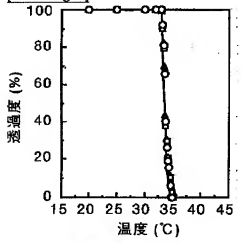
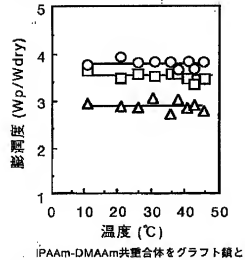
DRAWINGS

[Drawing 1]



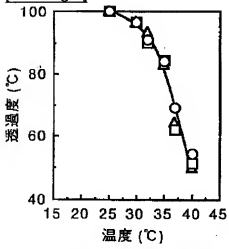
片末端にアミノ基を有するIPAAm-DMAAm共重合体の透過度の温度依存性：
(○) : 1a ; (□) :1b; (△) : 1c.

[Drawing 2]



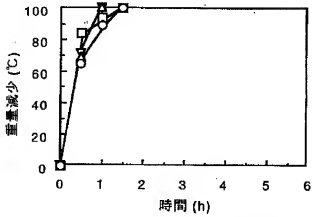
IPAAm-DMAAm共重合体をグラフト鎖とするDexヒドロゲルの膨潤度の温度依存性：
(○) : 3a ; (□) :3b; (△) : 3c.

[Drawing 3]



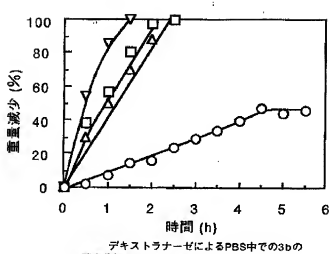
IPAAm-DMAAm共重合体をグラフト鎖とするDexヒドロゲルの透過度の温度依存性：(○) : 3a ; (□) :3b; (△) : 3c.

[Drawing 4]



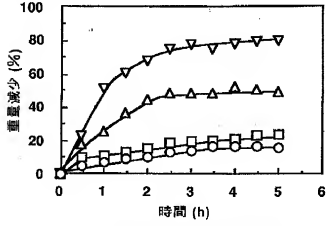
デキストラナーゼによるPBS中での3aの酵素分解：(○) : at 30 ℃ ; (□) : at 35°C; (△) : at 37°C; (▽) : at 40°C.

[Drawing 5]



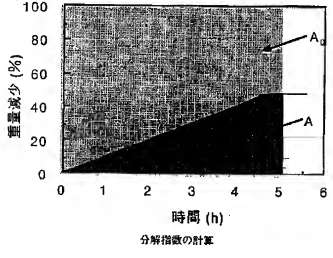
デキストラナーゼによるPBS中での3bの酵素分解：(○) : at 30 °C ; (□) : at 35°C; (△) : at 37°C; (▽) : at 40°C.

[Drawing 6]



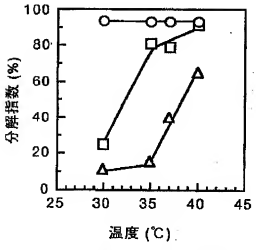
デキストラナーゼによるPBS中での3cの酵素分解：(○) : at 30 °C ; (□) : at 35°C; (△) : at 37°C; (▽) : at 40°C.

[Drawing 7]



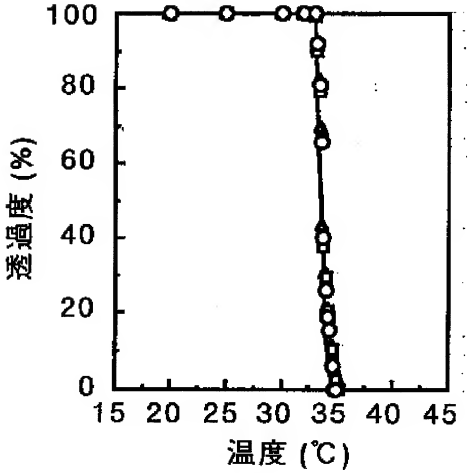
分解指数の計算

[Drawing 8]



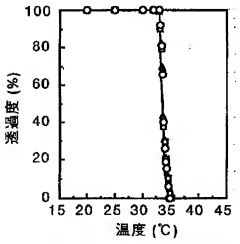
分解指数と温度との関係：(○)：3a；(□)：3b；(△)：3c.

[Translation done.]



片末端にアミノ基を有するIPAAm-DMAAm共重合体の透過度の温度依存性：
(○) : **1a**; (□) :**1b**; (△) : **1c**.

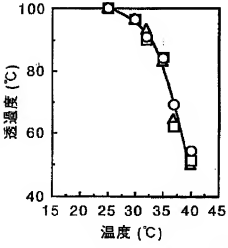
Drawing selection Drawing 2



片末端にアミノ基を有するIPAAm-DMAAm共重合体の透過度の温度依存性：(○)：1a；(□)：1b；(△)：1c.

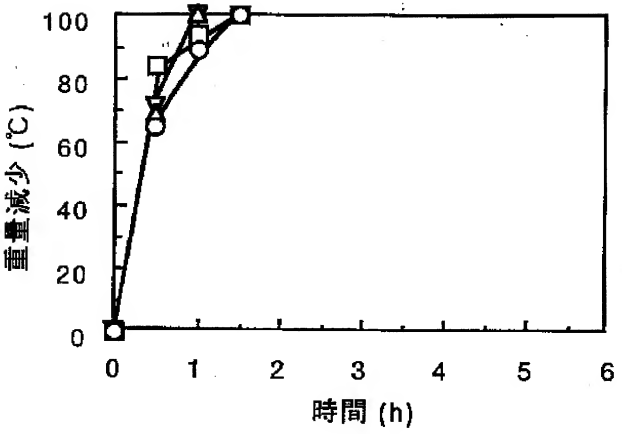
[Translation done.]

Drawing selection Drawing 3

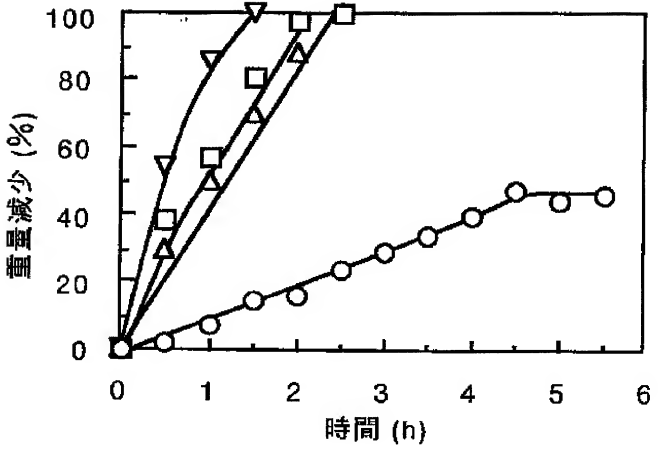


IPAAm-DMAAm共重合体をグラフト鎖とするDexヒドロゲルの透過度の温度依存性：(○)：3a；(□)：3b；(△)：3c.

[Translation done.]

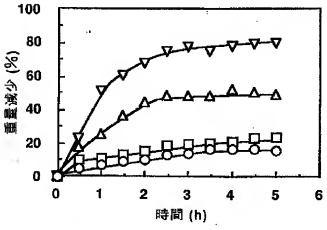


デキストラナーゼによるPBS中での3aの酵素分解：(○) : at 30 °C ; (□) : at 35°C; (△) : at 37°C; (▽) : at 40°C.



デキストラナーゼによるPBS中での3bの酵素分解：(○) : at 30 °C ; (□) : at 35°C; (△) : at 37°C; (▽) : at 40°C.

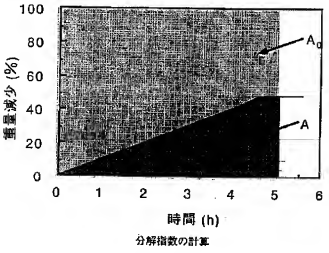
Drawing selection Drawing 6



デキストラナーゼによるPBS中での3cの酵素分解：(○) : at 30 °C ; (□) : at 35°C; (△) : at 37°C; (▽) : at 40°C.

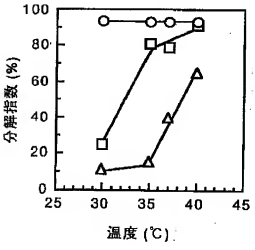
[Translation done.]

Drawing selection Drawing 7



[Translation done.]

Drawing selection Drawing 8



分解指数と温度との関係：(○)：3a；(□)：3b；(△)：3c.

[Translation done.]